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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/878,348	06/18/97	HEATH	A 2257-1-001

(H)

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EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1644	9

DATE MAILED: 02/08/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on 11/30/98

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-10, 12, 13, 15-23 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-10 12, 13, 15-23 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1644, Technology Center 1600.

2. Applicant's amendment, filed 11/30/98 (Paper No. 8), is acknowledged.
Claims 11 and 14 have been canceled.
Claims 1-3, 5, 12, 13, 15, and 17-22 have been amended.

claims 1-10, 12, 13, 15-23 are pending and under consideration.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed ½/98 (Paper No.).
The rejections of record can be found in the previous Office Action (Paper No.).

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84.
Please see the form PTO-948 previously sent in Paper No. 6.
Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes, if necessary.

5. Upon reconsideration of applicant's amended claims, filed 11/30/98 (Paper No. 8), the previous rejections under 35 U.S.C. § 112, first and second paragraphs, as they would apply to the recitation of "parts thereof" with respect to CD40-specific antibodies in the instant claims have been withdrawn.

6. Claims 1-4, 8-10, 12, 13, 15-23 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention essentially for the reasons of record set forth in Paper No. 6 with respect to the recitation of an "adjuvant which is adapted to stimulate a B lymphocyte cell surface receptor, CD40"

Applicant's arguments, filed 11/30/98 (Paper No. 8), have been fully considered but are not found convincing. Applicant argues that the instant specification provides suitable means for stimulating B cell: CD40 interactions with adjuvants and that the claims now distinctly claimed the invention.

In contrast to applicant's assertions, the claims do not distinctly set forth the metes and bounds or define an "adjuvant is adapted to stimulate a B lymphocyte cell surface receptor, CD40" and "parts thereof" as it applies to the CD40L.

While there is direction and guidance to CD40-specific antibodies and CD40 ligand; the defining structural features of the adjuvants are either not known or ill-defined and ambiguous. In addition, while "adjuvant" may have some notion of activity or structure, there is nothing in the claims which distinctly claims or sets forth the metes and bounds of the "adjuvant". Applicant has not enabled or provided sufficient written description of any "adjuvant which is adapted to stimulate a B lymphocyte cell surface receptor, CD40". It is noted the specification discloses that the instant adjuvant includes references to any string of amino acids or ligand which is selected so as to bind to at least a part of CD40 (page 8, paragraph 1). There is insufficient direction and guidance as well as written description as to the scope of such "string of amino acids". Further for the reasons set forth herein, it is not sufficient to simply bind to at least a part of CD40 to provide for adjuvant properties, as encompassed by the claimed invention. For example, there are both agonistic and antagonistic CD40-specific antibodies and agonistic antibodies need to be cross-linked in some manner to provide augmentation of the immune response and lymphocyte signaling.

With respect to the CD40 ligand, WO 93/08207 discloses that membrane bound CD40L and oligomeric CD40L (dimeric or trimeric) are useful as CD40 agonists, while monomeric CD40L is useful as a CD40 antagonist (see entire document, including page 12, paragraph 1). There appears insufficient guidance and enablement for the use of adjuvants comprising CD40 ligand, wherein the CD40L is not at least oligomeric and preferably trimeric. Mazzei et al. (J. Biol. Chem. 270: 7025, 1995); the trimeric conformation of the CD40 ligand may be required for binding to CD40 and its ability to stimulate via CD40 that is indistinguishable from the membrane bound from of the protein (see entire document, including Abstract and Discussion). While functional soluble forms of recombinant CD40L have been produced, it was known at the time the invention was made that a CD40L-IgG1-Fc fusion proteins which exists as a disulphide-linked dimer has low activity on B cells and required additional cytokines for B cell proliferation under defined culture conditions.

Therefore it would be expected that "parts" of CD40L or targeting only parts of CD40 (CD40 receptor) would not result in sufficient signaling associated with the claimed adjuvants. In contrast, it would be expected that "parts of CD40L or targeting "parts of CD40" would serve to antagonize the activity of lymphocyte responses. There appears insufficient guidance and direction as to enablement and written description of the claimed "adjuvants", "parts of CD40 ligand" or targeting "parts of CD40", commensurate in scope with the claimed invention. Applicant has not enabled such adjuvants with CD40L or antibodies that bind CD40 that do not have the appropriate conformation or sufficient multivalency to stimulate lymphocyte responses, associated with the properties of an adjuvant.

It was known at the time the invention was made that sufficient stimulation via CD40 required cross-linking of CD40 via CD40-specific antibodies or CD40 ligand in combination with appropriate lymphokines. In applying CD40 ligand, cross-linking occurred via transfected or surface-bound CD40 ligand. There is insufficient guidance and direction to enable adjuvants adapted to stimulate a B lymphocyte cell surface receptor CD40 and the production of said adjuvants other than providing CD40 ligand as oligomers and particularly trimers or polypeptides having the appropriate multivalency or providing CD40-specific antibodies in a manner that induces appropriate immune responses in vivo.

In view of the lack of predictability of the art to which the invention pertains the lack of established protocols for effective adjuvants, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed compositions and methods and absent working examples providing evidence which is reasonably predictive that the claimed compositions and methods are effective as an adjuvant.

The amendments must be supported by the specification so as not to add any new matter.

Applicant's arguments are not found persuasive.

7. Upon reconsideration of applicant's amended claims, filed 11/30/98 (Paper No. 8), the previous rejections under 35 U.S.C. § 112, second paragraph, as they would apply to the instant claims has been withdrawn.

8. Claims 1-3, 5-6, 8, 10, 12 are rejected under 35 U.S.C. § 102(a) as being anticipated by Dullforce et al. (1449, #AA). Dullforce et al. Teach vaccinating with CD40-specific antibodies and polysaccharide (see Abstract) essentially for the reasons of record set forth in Paper No. 6.

Applicant's arguments, filed 11/30/98 (Paper No. 8), have been fully considered but are not found convincing. Applicant argues that this reference represent applicant's own work; therefore it is not proper art. However, the prior art is "by another", which means other than applicant and is proper art.

Applicant may consider providing a Katz-type declaration by Heath to substantiate that this reference is applicant's own work as asserted to obviate this rejection.

Applicant's arguments are not found persuasive.

9. Upon reconsideration of applicant's amended claims, filed 11/30/98 (Paper No. 8), which now recite "where said adjuvant and said antigen are joined together"; the previous rejection under 35 U.S.C. § 102(a)(e) as being anticipated by Aruffo et al. (U.S. Patent No. 5,540,926), Armitage et al. (WO 93/08207) and Ledbetter et al. (U.S. Patent No. 5,247,069).

10. Claims 1-10, 12, 13 and 15-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Aruffo et al. (U.S. Patent No. 5,540,926) AND/OR Armitage et al. (WO 93/08207) AND/OR Ledbetter et al.(U.S. Patent No. 5,247,069) AND/OR Dullforce et al. (1449, #AA) in view of art known methods of making and providing vaccine formulations to various antigens, as acknowledged by applicant in their traverse response to the restriction requirement, filed 2/27/98 (Paper No. 5), as acknowledged by applicant's specification where it is stated that "it should be apparent to those skilled in the art that this methodology may also be applied to any antigens" (page 7, lines 1-2) and in view of Noelle (Immunity, 1996), Mond et al. (U.S. Patent No. 5,585,100), Scott et al. (U.S. Patent No. 5,723,127)Marburg et al. (U.S. Patent Nol. 5,623,057) essentially for the reasons of record set forth in Paper no. 6..

Applicant's arguments, filed 11/30/98 (Paper No. 8), have been fully considered but are not found convincing. Applicant arguments and the examiner's rebuttal concerning the applicability of Dullforce as prior art has been addressed above in section

Applicant argues that the secondary references do not cure the deficiencies of the primary references because Noelle et al. only suggests a role for CD40 ligand and its receptor in host defense; Mond et al. teaches a dual immunogenic carrier; Scott et al. teach the use of IL-12 as an adjuvant; and Marburg et al. teach a particular immunocarrier linked to pure polysaccharide. Applicant asserts MPEP 2143.01 to state that fact that references can be combined or modified is not sufficient to establish prima facie obviousness. Ap-plicant asserts that the claimed invention can only come from applicant's own disclosure.

In response to applicant's arguments, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

As pointed out in the last Office Action, Aruffo et al. AND/OR Armitage et al. AND/OR Ledbetter et al. AND/OR Dullforce et al. the use of CD40L or CD40-specific antibodies as adjuvants for vaccines or to boost immune responses in various individuals. They differ from the instant claims by not disclosing all of the art practiced methods and formulations of making said vaccines comprising an adjuvant nor do they disclose the art known combination of an adjuvant with an antigen of interest. Further and as noted above, both applicant's response to the restriction requirement and the specification as filed indicate that vaccine formulations and methods of making said vaccines comprising an adjuvant, as encompassed by the dependent claims were all well known and practiced by the ordinary artisan at the time the invention was made. It was clear that the primary references teach the use of CD40L or CD40-specific antibodies as adjuvants to stimulate the immune response, including B cells responses and that the various dependent limitations were all well known vaccine formulations and methods of making said vaccine formulations at the time the invention was made by the ordinary artisan. As well known and practiced at the time the invention was made, as acknowledged by applicant and as taught by the combination of primary and secondary references, the ordinary artisan had various means to make and formulate vaccines to a number of antigens, including both TD and TI antigens as well as the constructs comprising immunogenic compositions comprising an adjuvant and an antigen wherein said adjuvant and antigen are joined together. Given the importance of signaling via the CD40 pathway, the ordinary artisan would have had an expectation of success in stimulating immune responses to a variety of antigens and the motivation to provide CD40-specific adjuvants and antigens joined together as an art known efficient means to stimulate an effective immune responses.

Applicant's arguments are not found persuasive.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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February 2, 1999

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